All supplementary plots and tables show results for the following 7 sets of parameter values:

A) $\mu = 10^{-6}$, $\theta = 0.01$, $\lambda = 1/2$ and 2 dimensions. This is identical to the figures in the main text

B) $\mu = 10^{-4}$, $\theta = 1$, $\lambda = 1/2$ and 2 dimensions

C) $\mu = 10^{-6}$, $\theta = 0.01$, $\lambda = 2$ and 2 dimensions

D) $\mu = 10^{-6}$, $\theta = 0.01$, $\lambda = 1/4$ and 2 dimensions

E) $\mu = 10^{-6}$, $\theta = 0.01$, $\lambda = 1/2$ and 3 dimensions

F) $\mu = 10^{-6}$, $\theta = 0.01$, $\lambda = 1/2$ and 4 dimensions

G) $\mu = 10^{-6}$, $\theta = 0.01$, $\lambda = 1/2$ and 7 dimensions

**Figure S1.** Phenotypic distribution of homozygous alleles as in Figure 1 for all sets of parameter values. For simulations containing more than two dimensions (plots E-G), only the first two dimensions are shown.

**Figure S2.** Epistasis as a function of overdominance as in Figure 3 for all sets of parameter values.

**Figure S3.** Maximum pairwise distance statistic as in Figure 4 for all sets of parameter values.

**Figure S4.** Maximum distance from optimal trajectory statistic as in Figure 5 for all sets of parameter values.

**Figure S5.** Effective number of paths statistic as in Figure 6 for all sets of parameter values.

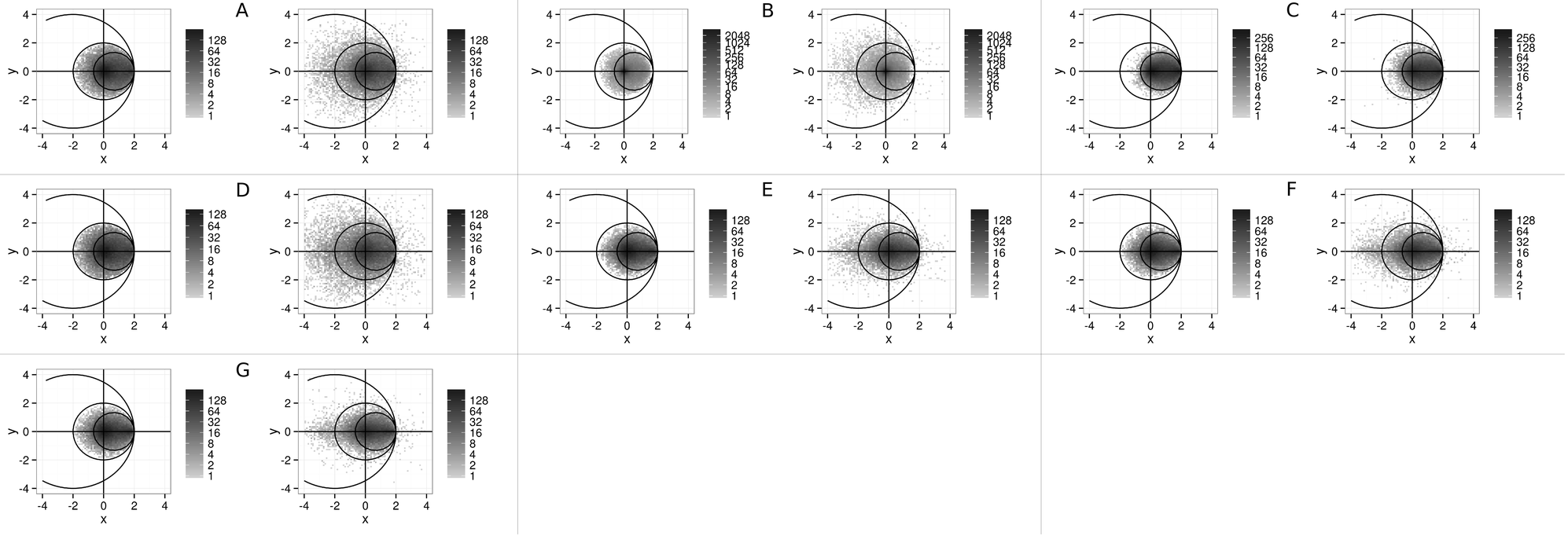
**Figure S6.** Mean path divergence statistic as in Lobkovsky et. al. (2011) for all sets of parameter values.

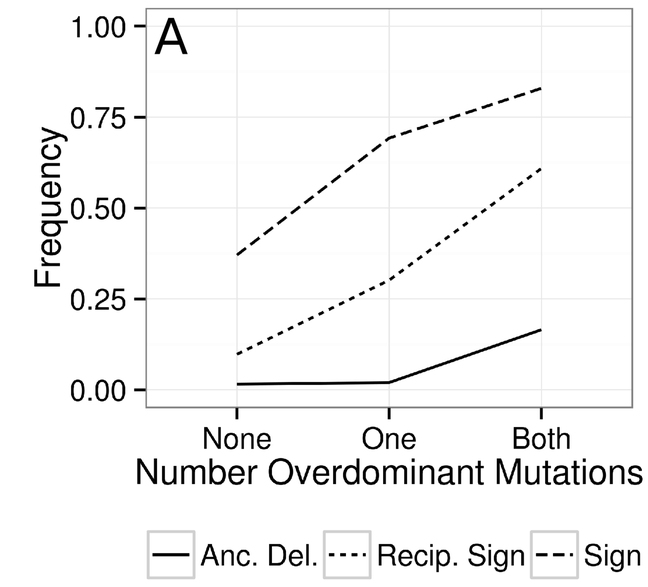
**Table S1.** Pairwise Epistasis (n=5,000)

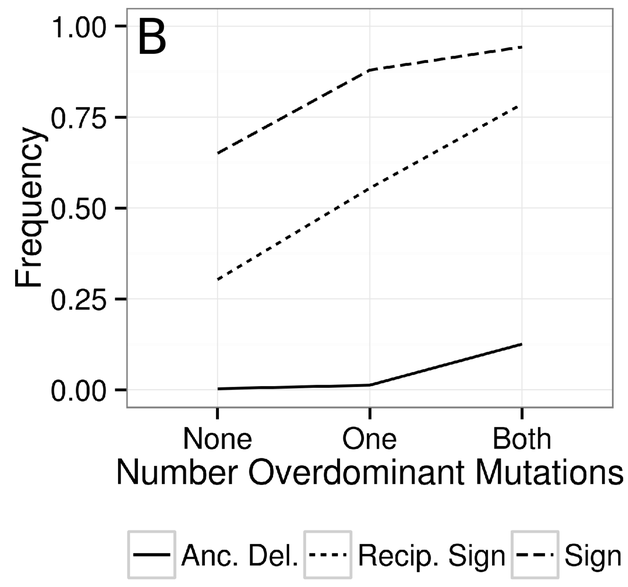
**Table S2.** Conditional Mutations

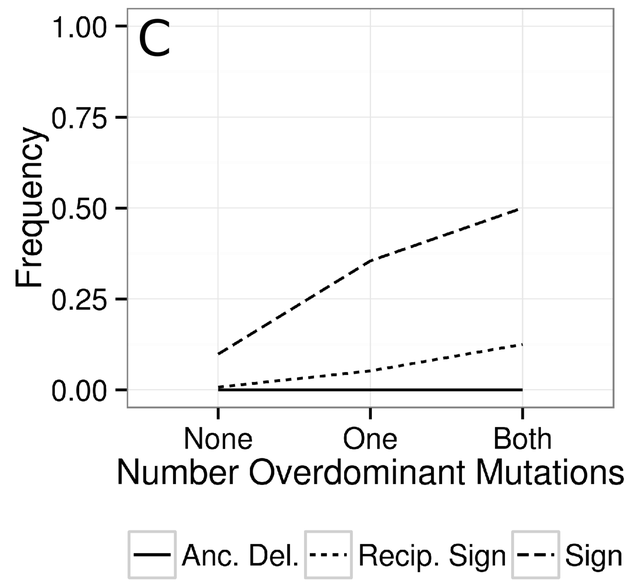
**Table S3.** Backwards Predictability P Values

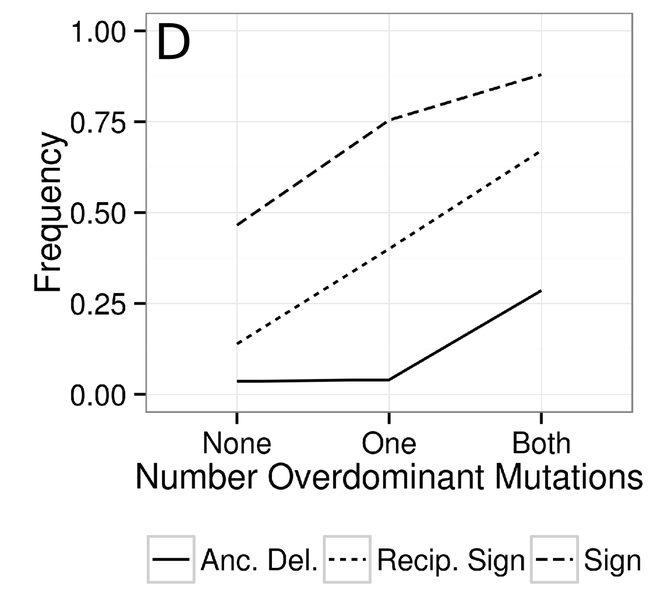
**Table S4.** Epistasis and Predictability P values

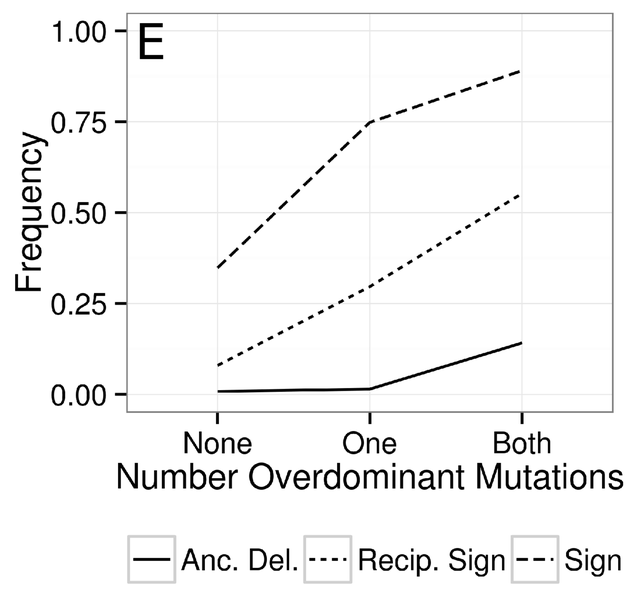

A
B
C
D
E
F
G
x
y
128
64
32
16
8
4
2
1
2048
1024
512
256
128
64
32
16
8
4
2
1
256
128
64
32
16
8
4
2
1

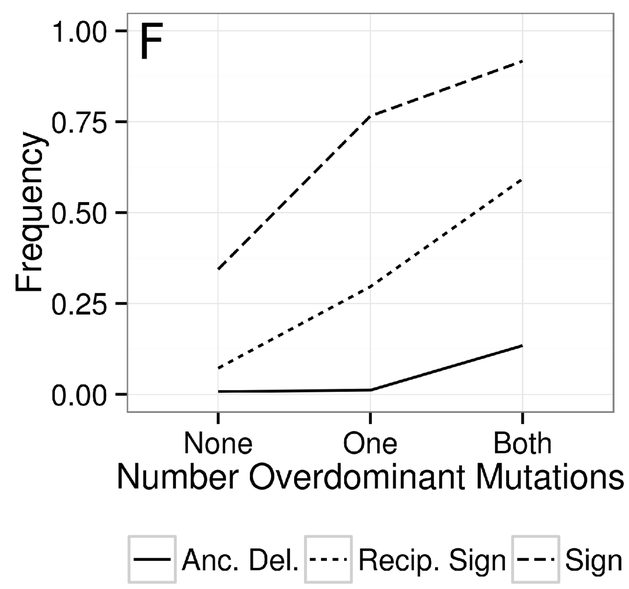

A
1.00
0.75
0.50
0.25
0.00
Frequency
None
One
Both
Number Overdominant Mutations
Anc. Del.
Recip. Sign
Sign

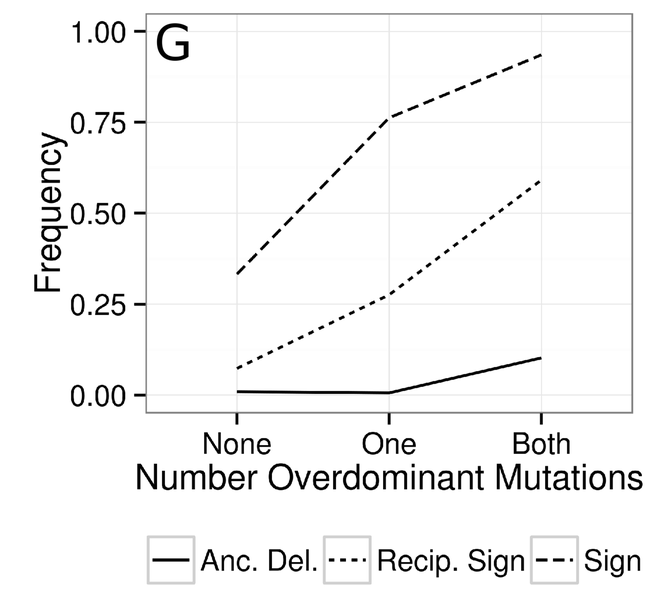

B
1.00
0.75
0.50
0.25
0.00
Frequency
None
One
Both
Number Overdominant Mutations
Anc. Del.
Recip. Sign
Sign


C
1.00
0.75
0.50
0.25
0.00
Frequency
None
One
Both
Number Overdominant Mutations
Anc. Del.
Recip. Sign
Sign

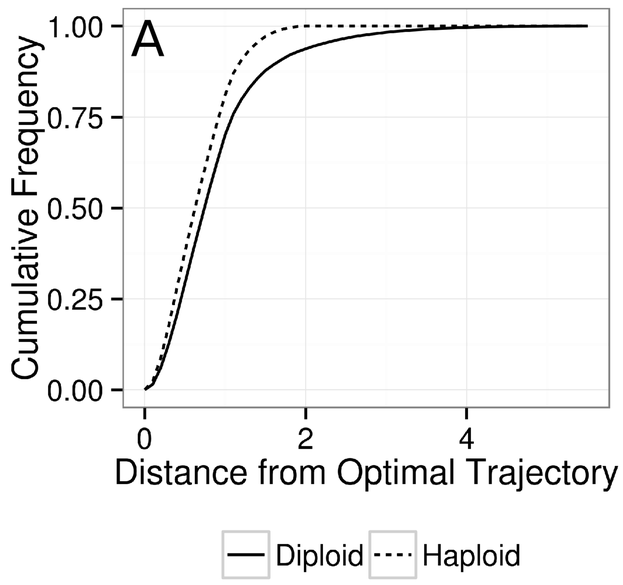

D
1.00
0.75
0.50
0.25
0.00
Frequency
None
One
Both
Number Overdominant Mutations
Anc. Del.
Recip. Sign
Sign

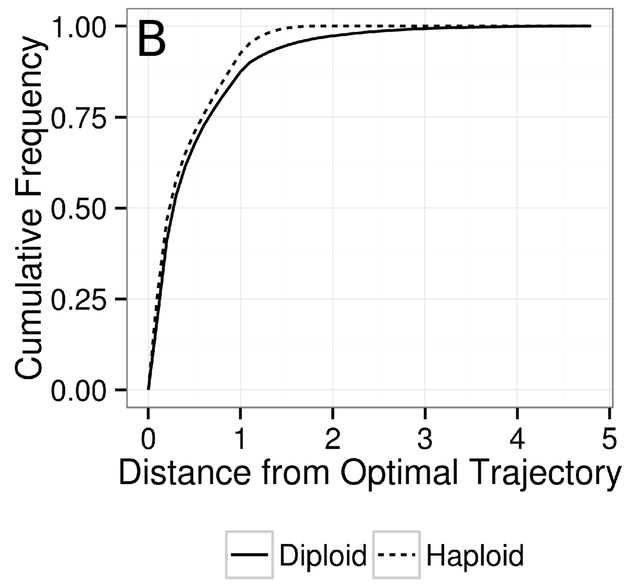

E
1.00
0.75
0.50
0.25
0.00
Frequency
None
One
Both
Number Overdominant Mutations
Anc. Del.
Recip. Sign
Sign

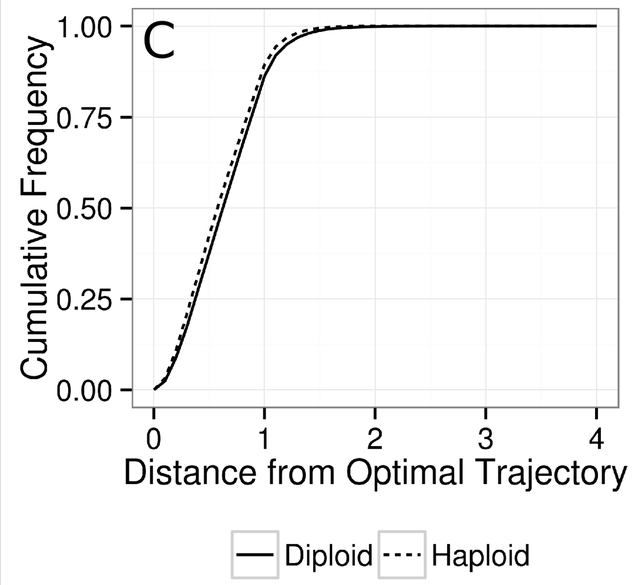

F
1.00
0.75
0.50
0.25
0.00
Frequency
None
One
Both
Number Overdominant Mutations
Anc. Del.
Recip. Sign
Sign

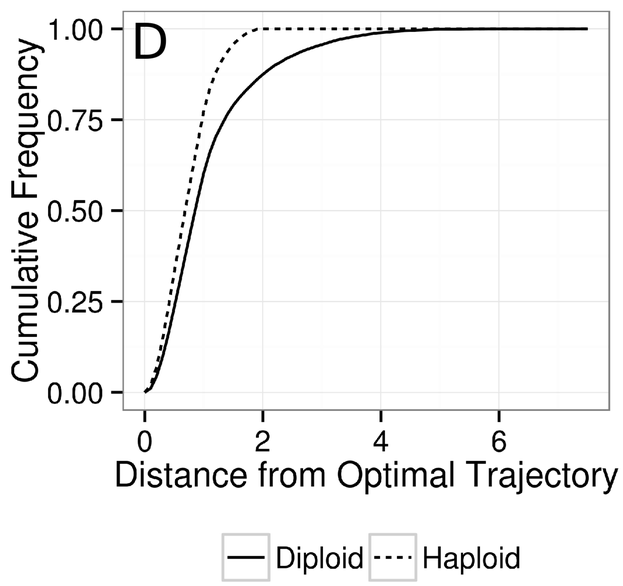

G
1.00
0.75
0.50
0.25
0.00
Frequency
None
One
Both
Number Overdominant Mutations
Anc. Del.
Recip. Sign
Sign

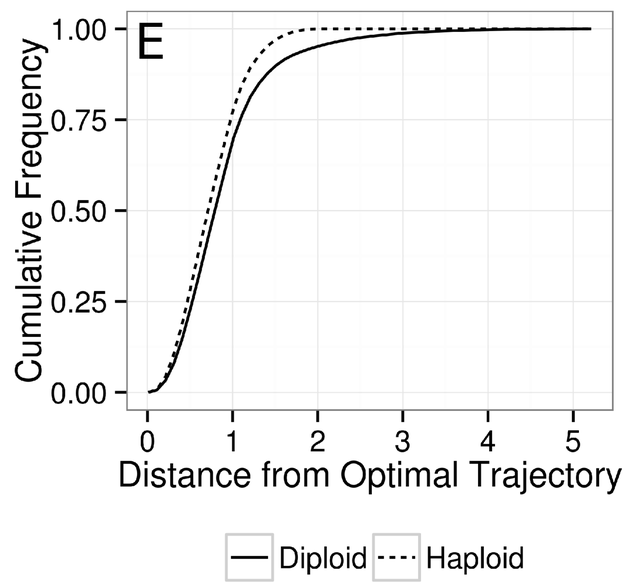
A
B
C
D
E
F
G
Cumulative Frequency
Max Pairwise Distance
Diploid
Haploid

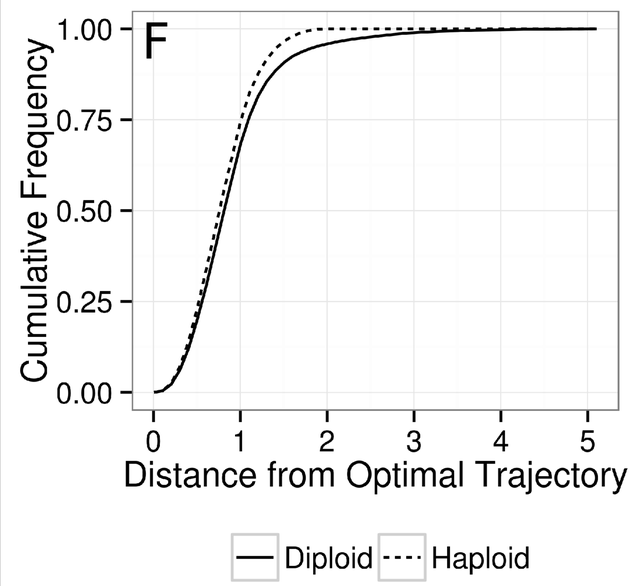

A
Cumulative Frequency
1.00
0.75
0.50
0.25
0.00
0
2
4
Distance from Optimal Trajectory
Diploid
Haploid

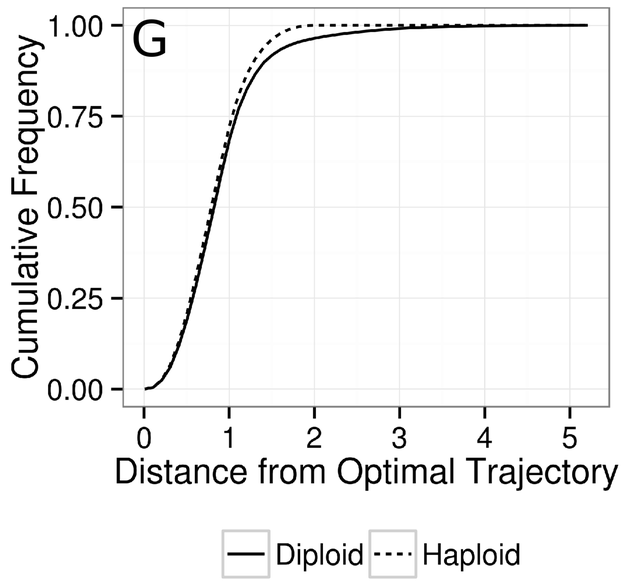

B
Cumulative Frequency
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
Distance from Optimal Trajectory
Diploid
Haploid

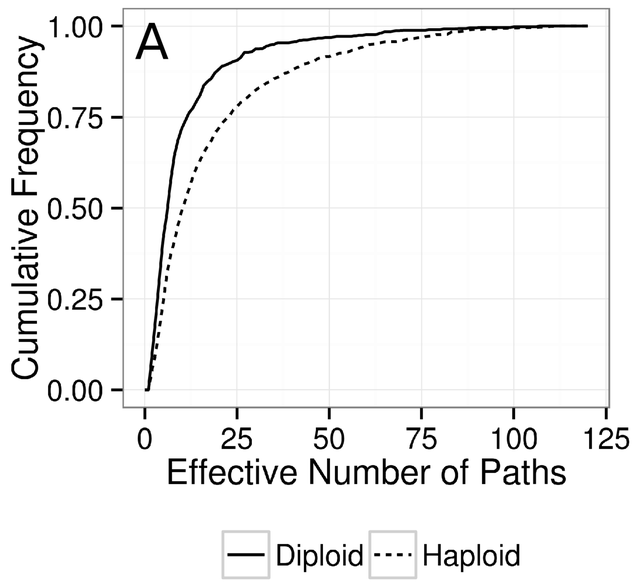

C
Cumulative Frequency
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
Distance from Optimal Trajectory
Diploid
Haploid

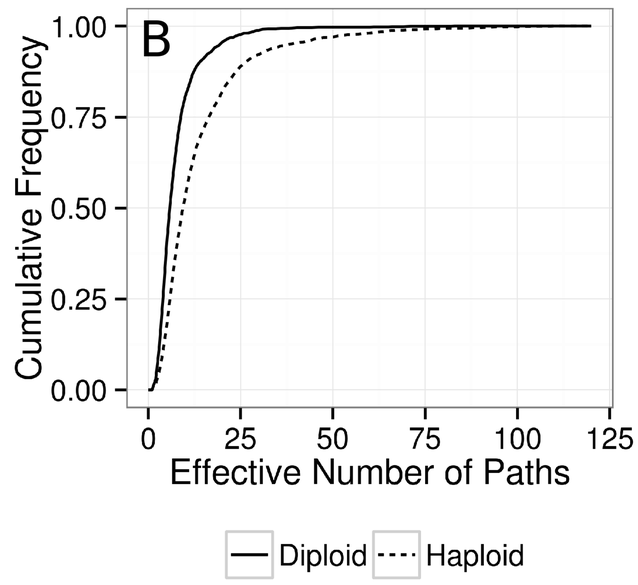

D
Cumulative Frequency
1.00
0.75
0.50
0.25
0.00
0
2
4
6
Distance from Optimal Trajectory
Diploid
Haploid

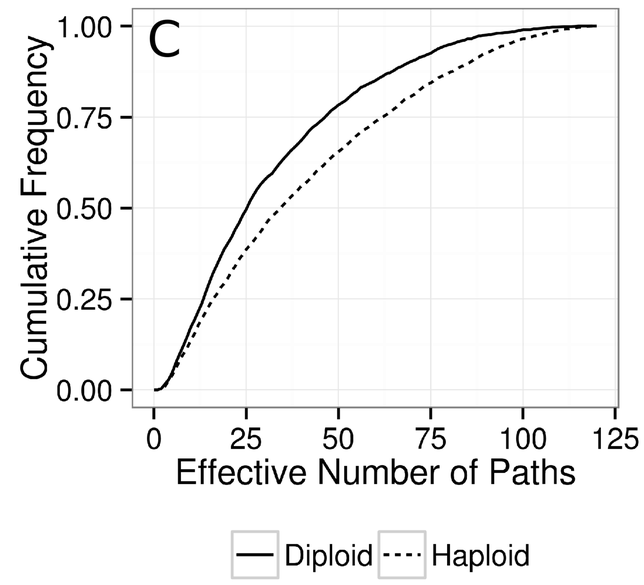

E
Cumulative Frequency
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
Distance from Optimal Trajectory
Diploid
Haploid

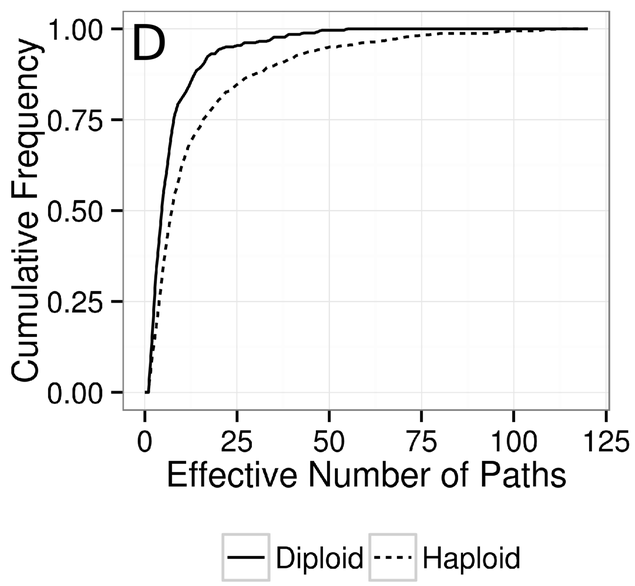

F
Cumulative Frequency
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
Distance from Optimal Trajectory
Diploid
Haploid

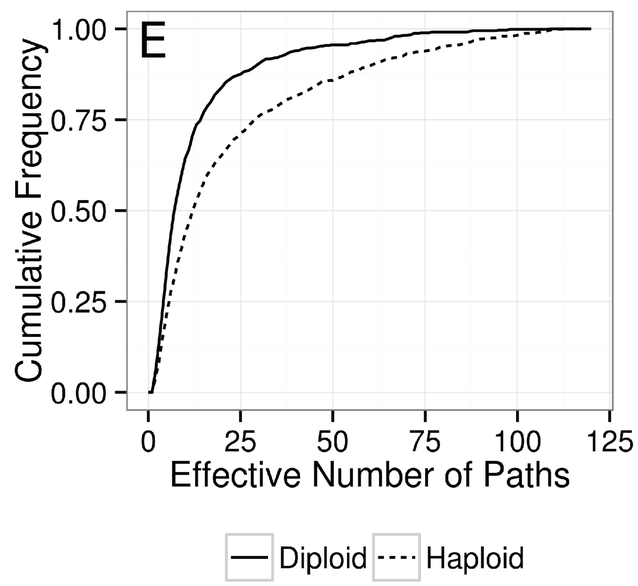

G
Cumulative Frequency
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
Distance from Optimal Trajectory
Diploid
Haploid

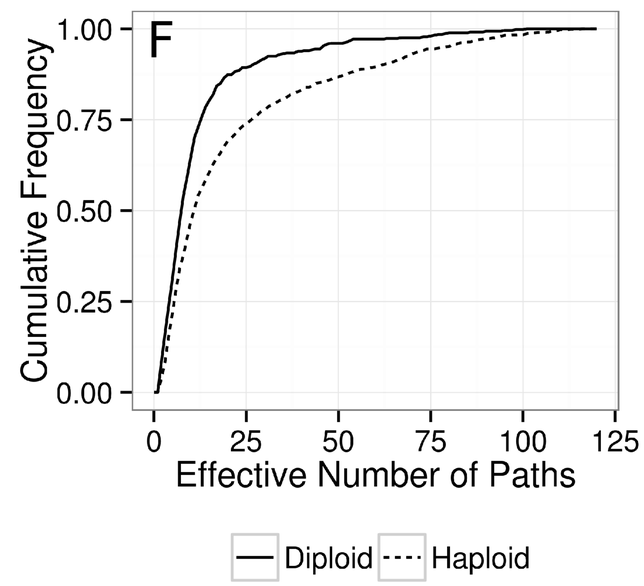

A
Cumulative Frequency
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
125
Effective Number of Paths
Diploid
Haploid

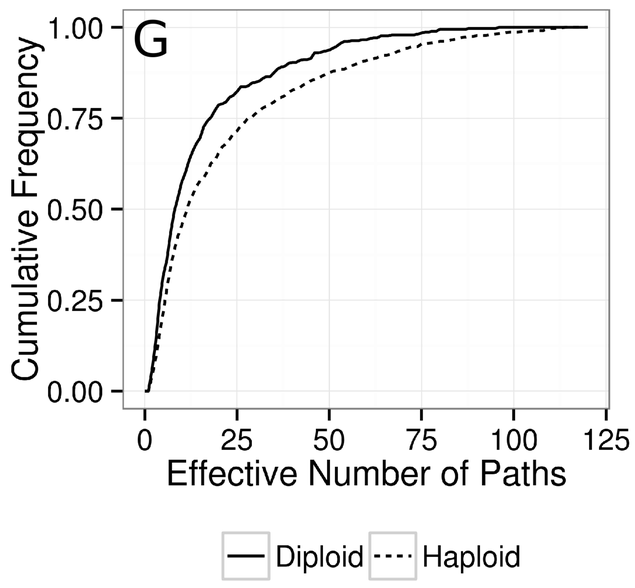

B
Cumulative Frequency
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
125
Effective Number of Paths
Diploid
Haploid


C
Cumulative Frequency
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
125
Effective Number of Paths
Diploid
Haploid


D
Cumulative Frequency
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
125
Effective Number of Paths
Diploid
Haploid


E
Cumulative Frequency
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
125
Effective Number of Paths
Diploid
Haploid


F
Cumulative Frequency
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
125
Effective Number of Paths
Diploid
Haploid


G
Cumulative Frequency
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
125
Effective Number of Paths
Diploid
Haploid

A
B
C
D
E
F
G
Cumulative Frequency
1.00
0.75
0.50
0.25
0.00
0.0
0.5
1.0
1.5
0.4
0.8
1.2
1.6
Mean Path Divergence
Diploid
Haploid

Table S1

| Parameter | χ2 p-value | Ploidy | Sign | Reciprocal Sign | Ancestral Deleterious |
|---|---|---|---|---|---|
| A | 8.8E-128 | Haploid | 52.30% | 31.00% | 16.00% |
| | | Diploid | 53.00% | 21.40% | 2.80% |
| B | 5.8E-252 | Haploid | 74.70% | 68.80% | 47.20% |
| | | Diploid | 76.40% | 65.10% | 6.20% |
| C | 1.3E-015 | Haploid | 12.60% | 3.50% | 0.80% |
| | | Diploid | 12.00% | 1.30% | 0.00% |
| D | 2.8E-151 | Haploid | 61.40% | 51.00% | 38.00% |
| | | Diploid | 65.80% | 49.40% | 17.20% |
| E | 7.7E-125 | Haploid | 53.20% | 38.10% | 23.00% |
| | | Diploid | 51.40% | 26.70% | 3.30% |
| F | 3.3E-139 | Haploid | 52.90% | 38.00% | 23.80% |
| | | Diploid | 50.60% | 25.40% | 2.90% |
| G | 2.5E-145 | Haploid | 54.20% | 38.90% | 24.50% |
| | | Diploid | 48.80% | 23.20% | 2.20% |

Table S2

| Parameter | χ2 p-value | Ploidy | All | Initial Mutation Overdominant | Initial Mutation Not Overdominant |
|---|---|---|---|---|---|
| A | 1.50E-14 | Haploid | 21.4% | NA | NA |
| | | Diploid | 26.3% | 62.4% | 18.2% |
| B | 1.30E-79 | Haploid | 48.1% | NA | NA |
| | | Diploid | 40.8% | 82.9% | 30.4% |
| C | 4.50E-06 | Haploid | 3.4% | NA | NA |
| | | Diploid | 4.6% | 27.2% | 3.7% |
| D | 2.80E-34 | Haploid | 27.4% | NA | NA |
| | | Diploid | 36.1% | 65.5% | 28.0% |
| E | 1.40E-07 | Haploid | 18.3% | NA | NA |
| | | Diploid | 21.5% | 61.4% | 14.0% |
| F | 8.20E-05 | Haploid | 17.4% | NA | NA |
| | | Diploid | 19.7% | 61.9% | 12.1% |
| G | 9.46E-01 | Haploid | 17.6% | NA | NA |
| | | Diploid | 17.5% | 60.9% | 10.3% |

Table S3

| | | N | extra mutations | final homozygote advantageous | observed path viable | other paths viable | observed path top 50% most likely | observed path most likely |
|---|---|---|---|---|---|---|---|---|
| A | Diploid | 645 | 57.98% | 99.53% | 92.87% | 98.91% | 80.78% | 16.74% |
| | Haploid | 1220 | 7.54% | 100.00% | 100.00% | 98.44% | 69.75% | 14.10% |
| B | Diploid | 2031 | 99.90% | 100.00% | 97.49% | 99.75% | 93.30% | 38.70% |
| | Haploid | 2295 | 91.94% | 100.00% | 99.56% | 99.78% | 96.47% | 34.77% |
| C | Diploid | 2286 | 45.98% | 99.96% | 99.34% | 100.00% | 71.39% | 3.85% |
| | Haploid | 2627 | 12.18% | 100.00% | 100.00% | 100.00% | 67.34% | 4.76% |
| D | Diploid | 263 | 48.67% | 98.10% | 90.11% | 98.10% | 80.23% | 20.91% |
| | Haploid | 679 | 3.68% | 100.00% | 100.00% | 97.50% | 67.16% | 17.38% |
| E | Diploid | 555 | 64.86% | 99.46% | 91.53% | 97.84% | 76.58% | 12.97% |
| | Haploid | 1283 | 6.31% | 100.00% | 99.92% | 98.99% | 66.17% | 10.44% |
| F | Diploid | 456 | 63.82% | 99.78% | 93.42% | 98.90% | 75.00% | 12.28% |
| | Haploid | 1164 | 5.50% | 100.00% | 100.00% | 99.23% | 66.41% | 12.63% |
| G | Diploid | 388 | 62.11% | 99.48% | 93.04% | 98.97% | 74.23% | 11.60% |
| | Haploid | 1008 | 5.56% | 100.00% | 100.00% | 99.31% | 64.29% | 10.71% |

Table S4

P values from chi-square contingency table tests

| | Hap vs Dip across all 4 levels of Epistasis | Diploid Sign Epi. One overdom vs no overdom | Diploid recip sign epi one overdom vs no overdom | Diploid anc del epi one overdom vs no overdom | Diploid sign epi two overdom vs no overdom | diploid recip sign epi two overdom vs no overdom | Diploid anc del epi two overdom vs no overdom | conditional mutation haploid vs diploid | initial mutation vs diploid not overdom initial mutation |
|---|---|---|---|---|---|---|---|---|---|
| A | 8.84E-128 | 2.03E-103 | 6.20E-70 | 3.20E-01 | 2.37E-61 | 2.02E-137 | 4.75E-49 | 1.52E-14 | 2.09E-290 |
| B | 5.80E-252 | 2.23E-71 | 1.50E-66 | 2.36E-04 | 3.93E-28 | 2.55E-69 | 5.87E-59 | 1.28E-79 | 0.00E+00 |
| C | 1.34E-15 | 5.72E-54 | 6.21E-16 | 0.00E+00 | 1.31E-03 | 7.47E-02 | 0.00E+00 | 4.53E-06 | 1.15E-100 |
| D | 2.75E-151 | 8.36E-85 | 1.42E-80 | 4.95E-01 | 3.50E-77 | 6.26E-155 | 1.11E-76 | 2.80E-34 | 1.90E-177 |
| E | 7.71E-125 | 3.76E-157 | 1.70E-86 | 5.70E-02 | 1.29E-56 | 5.26E-101 | 2.28E-46 | 1.39E-07 | 0.00E+00 |
| F | 3.27E-139 | 6.21E-168 | 1.17E-94 | 2.66E-01 | 1.43E-62 | 4.06E-127 | 1.22E-44 | 8.25E-05 | 0.00E+00 |
| G | 2.51E-145 | 6.20E-171 | 2.71E-80 | 2.99E-01 | 1.99E-61 | 5.47E-114 | 4.87E-24 | 9.46E-01 | 0.00E+00 |

p values from two-tailed t tests

| | max pairwise dist p value | max dist from optimal p value | Dip vs Hap Effective num paths p valuje | cor dip effective num paths and num overdom | cor p value dip effective num paths and num overdom | mean path divergence p value |
|---|---|---|---|---|---|---|
| A | 9.97E-22 | 0.00E+00 | 4.06E-20 | -0.345 | 1.40E-19 | 4.89E-10 |
| B | 1.36E-66 | 7.66E-220 | 1.38E-79 | -0.302 | 2.15E-44 | 3.45E-40 |
| C | 4.98E-27 | 4.21E-91 | 5.12E-31 | -0.425 | 4.52E-101 | 5.11E-12 |
| D | 6.42E-21 | 0.00E+00 | 3.31E-15 | -0.282 | 1.86E-06 | 4.42E-06 |
| E | 4.42E-17 | 0.00E+00 | 2.15E-23 | -0.393 | 6.80E-22 | 5.63E-09 |
| F | 9.75E-07 | 3.71E-196 | 6.41E-19 | -0.331 | 2.68E-13 | 1.63E-07 |
| G | 3.94E-04 | 7.81E-111 | 3.86E-09 | -0.287 | 4.68E-09 | 9.85E-04 |